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(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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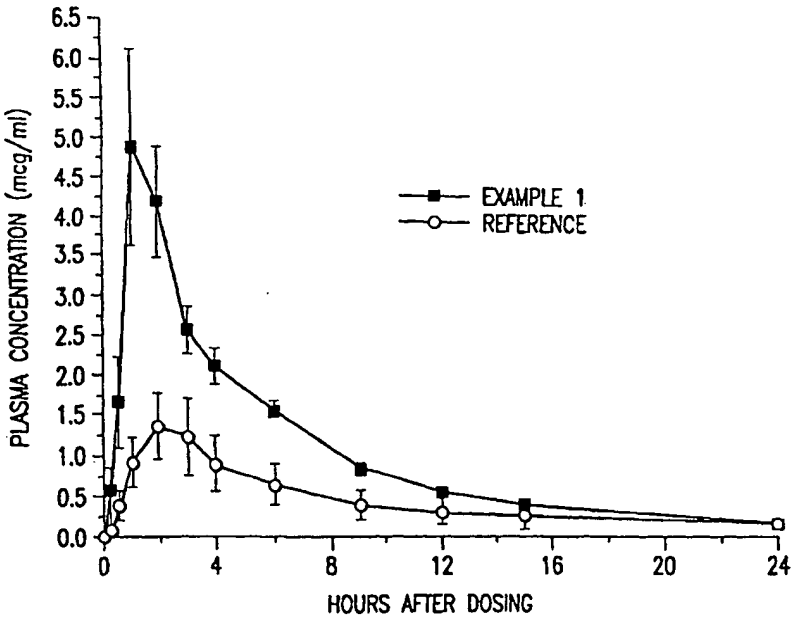
(54) Title: NOVEL FORMULATIONS COMPRISING LIPID–REGULATING AGENTS



(57) Abstract

The present invention is directed to a formulation comprising a lipid–regulating agent dissolved in a mixture of an oil and one or more surfactants to form a concentrate. This concentrate forms fine and stable emulsions upon gentle mixing with water or any aqueous solutions.

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Novel Formulations Comprising Lipid-Regulating Agents

Field of the Invention

The present invention relates to novel formulations comprising lipid-regulating agents.

Background of the Invention

2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid, 1-methylethylester, also known as fenofibrate, is representative of a broad class of compounds having pharmaceutical utility as lipid regulating agents. More specifically, this compound is part of a lipid-regulating agent class of compounds commonly known as fibrates, and is disclosed in U.S. Patent No. 4,058,552.

Fenofibrate has been prepared in several different formulations, c.f., U.S. Patent No. 4,800,079 and U.S. Patent No. 4,895,726. U.S. Patent No. 4,895,726 discloses a co-micronized formulation of fenofibrate and a solid surfactant.

U.S. Patent No. 4,961,890 discloses a process for preparing a controlled release formulation containing fenofibrate in an intermediate layer in the form of crystalline microparticles included within pores of an inert matrix. The formulation is prepared by a process involving the sequential steps of dampening said inert core with a solution based on said binder, then projecting said fenofibrate microparticles in a single layer onto said dampened core, and thereafter drying, before said solution based on said binder dissolves said fenofibrate microparticles, and repeating said three steps in sequence until said intermediate layer is formed.

European Patent Application No. EP0793958A2 discloses a process for producing a fenofibrate solid dosage form utilizing fenofibrate, a surface active agent and polyvinyl pyrrolidone in which the fenofibrate particles are mixed with a polyvinyl pyrrolidone solution. The thus obtained mixture is granulated with an aqueous solution of one or more surface active agents, and the granulate thus produced is dried.

PCT Publication No. WO 82/01649 discloses a fenofibrate formulation having granules that are comprised of a neutral core that is a mixture of saccharose and starch. The neutral core is covered with a first layer of fenofibrate, admixed with an excipient and with a second microporous outer layer of an edible polymer.

U.S. Patent No. 5,645,856 describes the use of a carrier for hydrophobic drugs, including fenofibrate, and pharmaceutical compositions based thereon. The carrier comprises a digestible oil and a pharmaceutically-acceptable surfactant component for dispersing the oil in vivo upon administration of the carrier, which comprises a hydrophilic surfactant, said surfactant component being such as not to substantially inhibit the in vivo lipolysis of the digestible oil.

Gemfibrozil is another member of the fibrate class of lipid-regulating agents. U.S. Patent No. 4,927,639 discloses a disintegratable formulation of gemfibrozil providing both immediate and sustained release, comprising a tablet compressed from a mixture of a first and second granulation, and a disintegration excipient operable to effect partial or complete disintegration in the stomach. The first granulation comprises finely divided particles of pure gemfibrozil granulated with at least one cellulose derivative, and the second granulation comprises finely

divided particles of pure gemfibrozil granulated with a pharmaceuitcally-acceptable water soluble or insoluble polymer which are then uniformly coated with a pharmaceuitcally-acceptable (meth)acylate copolymer prior to admixture with the first granulation. The first and second granulations are present in the final composition in a ratio of from about 10:1 to about 1:10.

U.S. Patent 4,925,676 discloses a disintegratable gemfibrozil tablet providing both immediate and enteric release, which is compressed from a mixture of a first granulation of gemfibrozil with at least one acid-disintegratable binder, and a second granulation formed from the first granulation, but regranulated or coated with an alkali-disintegratable formulation of at least one substantially alkali-soluble and substantially acid-insoluble polymer.

Another class of lipid-regulating agents are commonly known as statins, of which pravastatin and atorvastatin are members. U.S. Patents 5,030,447 and 5,180,589 describe stable pharmaceutical compositions, which when dispersed in water have a pH of at least 9, and include a medicament which is sensitive to a low pH environment, such as prevastatin, one or more fillers such as lactose and/or microcrystalline cellulose, one or more binders, such as microcrystalline cellulose (dry binder) or polyvinylpyrrolidone (wet binder), one or more disintegrating agents such as croscarmellose sodium, one or more lubricants such as magnesium stearate and one or more basifying agents such as magnesium oxide.

It is an object of the present invention to provide formulations of lipid-regulating agents having enhanced bioavailability and longer half-life when compared to commercially available formulations.

Summary of the Invention

The present invention is directed to a formulation comprising a lipid-regulating agent dissolved in a mixture of an oil and one or more surfactants to form a concentrate. This concentrate forms fine and stable emulsions upon gentle mixing with water or any aqueous solutions. The emulsions result in an increase in drug solubility and oral bioavailability.

The formulation may be administered directly, diluted into an appropriate vehicle for administration, encapsulated into soft or hard gelatin capsules for administration, or administered by other means obvious to those skilled in the art.

Brief Description of the Drawings

Figure 1 is a graph showing the plasma concentration in fasted dogs of the formulation of Example 1 and a reference compound.

Detailed Description of the Invention

The bulk lipid-regulating agent may be prepared by any available method, as for example the compound fenofibrate may be prepared by the procedure disclosed in U.S. Patent No. 4,058,552, or the procedure disclosed in U.S. Patent No. 4,739,101, both herein incorporated by reference.

The solution comprising the lipid-regulating agent is prepared by premixing the oil and one and more surfactants, then adding the lipid-regulating agent to the premix and mixing the resulting mixture well until dissolved.

The delivery system of the present invention results in increased solubility, half-life and bioavailability of the lipid-regulating agent. It can be further diluted with additional liquids or it may be thickened and/or stabilized with various pharmaceutical excipients to vary its existing properties.

Suitable oils include, but are not limited to, any pharmaceutically acceptable oil, such as, for example, Myvacet 9-08 (distillated acetylated monoglycerides: manufacturer), Myvacet 9-40 (distillated acetylated monoglycerides: manufacturer), Capmul PG-8 (propylene glycol and mono/di-caprylate; Abitec), Arlamol E (polyoxypropylene (15) stearyl alcohol; ICI), Captex 300 (glyceryl tricaprylate/caprate; Abitec), Labrafac Lipophile WL 1349 (triglyceride of caprylic/capric acid; Gattefosse), olive oil, Miglyol 812 ((caprylic/capric triglycerides; HULS America), sesame oil, Novol (oleyl alcohol; Croda). Preferred oils include Myvacet 9-08, Myvacet 9-40, and Capmul PG-8

Suitable surfactants include any surfactant in which fenofibrate is highly soluble. Such surfactants will typically be those with HLB values ranging from about 1 to about 20. Representative surfactants include Labrafac Lipophile WL 1349 (triglyceride of caprylic/capric acid; Gattefosse), Lauroglycol FCC (propylene glycol laurate; Gattefosse), Labrafil M 1944 CS (glyceryl and polyethylene glycol esters; Gattefosse), Span 80 (sorbitan monooleate; Sigma), Capmul MCM (mono/diglycerides of caprylic/capric acid in glycerol; Abitec), Arlacel 83 (sorbitan sesquioleate; ICI), Brij 93 (polyoxyethylene (2) oleyl ether; READ ICI), Acconon E (polyoxypropylene 15 stearyl ether; Abitec), Labrafil M 2125 CS (unsaturated polyglycolyzed glycerides; Gattefose), Maisine 35-1 (glyceryl monolinoleate; Gattefosse), Sorbitan Oleate NF (Crill #4; Croda), Caprol 10G100 (decaglyceryl decaoleate;

Abitec), Labrafil Isostearique (triisostearin PEG 6 esters; Gattefosse), Caprol 3G0 triglyceryl monoleate; Abitec), Peceol (glyceryl monooleate; Gattefosse), G-950 (sorbide dioleate; ICI), Arlacel 989 (polyoxyethylene castor wax; ICI), Labrafac CM 10 (polyglycolysed glycerides; Gattefosse), Labrafac CM 12 (polyglycolysed glycerides; Gattefosse), Labrasol (saturated C8-C10 polyglycolysed glycerides; Gattefosse), Tween 80 (polyoxyethylene (20) sorbitan monooleate; Sigma), Tween 85 (polyoxyethylene (20) sorbitan trioleate; Sigma), Pluronic L43 (copolymers of propylene oxide and ethylene oxide; BASF), Pluronic 17R4 (copolymers of propylene oxide and ethylene oxide; BASF), Cremophor EL (polyoxyl 35 castor oil; BASF), Accomid PK (palm kernelamide DEA; Abitec), Brij 30 (polyoxyethylene 4 lauryl ether; READ ICI), Arlasolve 200 liquid (polyoxyethylene (20) isohexadecyl ether; ICI), Arlacel 20 (sorbitan monolaurate; ICI), Renex 38 (alcohol ethoxylate; ICI), G-4280 (polyoxyethylene 80 sorbitan monolaurate; ICI), Caprol 6G20 (hexaglyceryl dioleate; Abitec), Crillet 4 Ultra (polysorbate 80; Croda), Crodesta SL-40 (sucrose laurate; Croda), Cirrasol G-265 (quaternary ammoniun salt; ICI), Cirrasol G-1096 (polyoxyethylene sorbitol hexaoleate; ICI), Softigen 767 (caprylic/capric acid partial glyceride-6 EO; HULS America), Witconol 14 (polyglyceryl 4 oleate; Witco).

Preferred surfactants include Labrafac Lipophile WL 1349 (triglyceride of caprylic/capric acid; Gattefosse), Labrofac CM 10 and CM 12(polyglycolysed glycerides; Gattefosse), Lauroglycol FCC (propylene glycol laurate; Gattefosse), Peceol (glyceryl monooleate; Gattefosse), Caprol 3G0 (triglyceryl monoleate; Abitec), Capmul MCM (mono/diglycerides of caprylic/capric acid in glycerol; Abitec), Labrasol (saturated C8-C10 polyglycolysed glycerides; Gattefosse), Tween 80 (polyoxyethylene (20) sorbitan monooleate; Sigma), Pluronic L43 (copolymers of propylene oxide; BASF), Pluronic 17R4 (copolymers of propylene oxide and ethylene oxide; BASF), Cremophor EL

(polyoxyl 35 castor oil; BASF), Brij 30 (polyoxyethylene 4 lauryl ether; READ ICI), Arlacel 20 (sorbitan monolaurate; ICI), Renex 38 (alcohol ethoxylate; ICI).

Other optional ingredients which may be included in the compositions of the present invention are those which are conventionally used in oil-based drug delivery systems, e.g. antioxidants such as, for example, tocopherol, ascorbyl palmitate, ascorbic acid, butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate, etc.; pH stabilizers such as, for example, citric acid, tartaric acid, fumaric acid, acetic acid, glycine, arginine, lysine, potassium hydrogen phosphate, etc.; thickeners/suspending agents such as, for example, hydrogenated vegetable oils, beeswax, colloidal silicon dioxide, gums, celluloses, silicates, bentonite, etc.; flavoring agents such as, for example, cherry, lemon, aniseed flavors, etc.; sweeteners such as, for example, aspartame, saccharin, cyclamates, etc.; and co-solvents, such as, for example, ethanol, propylene glycol, polyethylene glycol, dimethyl isosorbide, etc.; adsorbents such as, for example, lactose, sorbitol, high molecular weight polyethylene glycols, such as, for example, PEG 1475,PEG 8000, etc.), and hydrophilic polymers, such as, for example, Avicel PH 101 (microcrustalline cellulose; FMC) hydroxypropylmethyl cellulose, etc.

The resulting liquid comprising the lipid-regulating agent may be dosed directly for oral administration, diluted into an appropriate vehicle for oral administration, filled into soft or hard shells or capsules for oral administration, or delivered by some other means obvious to those skilled in the art. The said liquid can be used to improve the oral bioavailability and solubility of the said lipid-regulating agent.

The invention will be understood more clearly from the following non-limiting representative examples:

Example 1

Myvacet 9-08 (40.2 gm) was mixed with propylene glycol laurate (13.4 gm). Fenofibrate (6.7 gm) was then added to the above mixture and mixed until completely dissolved. One drop of the solution was diluted with 10 ml of water and the droplet size was measured by laser light scattering as 2.95 (m. 670 mg of the mixture (containing 67 mg of fenofibrate) was added to each soft gelatin capsule.

Example 2

Myvacet 9-08 (40.2 g) is mixed with propylene glycol laurate (13.4 g). Pravastatin (5.0 g) is then added to the above mixture and mixed until well dissolved. Appropriate amount of solution may be filled into capsules to provide the desired dose.

Example 3

The emulsion prepared by the process described in Example 1, and from a commercial fenofibrate composition, Lipanthyl 67M (Groupe Fournier) (Reference), were administered to a group of dogs at a dose of 67 mg fenofibrate/dog (10 mL emulsion or one capsule/dog). The plasma concentrations of fenofibric acid were determined by HPLC. Concentrations were normalized to a 6.7 mg/kg dose in each dog. Figure 1 presents the resulting data in graph form. The results provided as mean ± SD, n=6, were as follows:

Lipanthyl 67M (Reference):
Cmax = 1.88 ± 0.97 mcg/ml
Tmax = 1.6 ± 0.9 hr
t1/2 = 4.5 hr
AUC (0-24) = 11.08 ± 9.42 mcg•hr/ml

Capsules of Example 1:

Cmax = 3.88 ± 2.15 mcg/ml

Tmax = 0.9 ± 0.3 hr

t1/2 = 5.9 hr

AUC (0-24) = 17.37 ± 10.58 mcg•hr/ml

Cmax relative to Reference = 2.1

AUC relative to Reference = 1.6

Claims

1. A composition comprising a lipid-regulating agent dissolved in at least one oil with one or more surfactants, wherein the mixture is capable of forming an emulsion upon dilution with an aqueous phase.

2. A composition of claim 1 wherein said lipid-regulating agent is a fibrate.

3. A composition of claim 2 wherein said fibrate is fenofibrate.

4. A composition of claim 1 wherein said lipid-regulating agent is a statin.

5. A composition of claim 4 wherein said statin is prevastatin.

6. A composition of claim 4 wherein said statin is atorvastatin.

7. A composition of claim 1 wherein at least one or more of said surfactants is triglyceride of caprylic/capric acid, propylene glycol laurate, glyceryl and polyethylene glycol esters, sorbitan monooleate, mono/diglycerides of caprylic/capric acid in glycerol, sorbitan sesquioleate, polyoxyethylene (2) oleyl ether, polyoxypropylene 15 stearyl ether, unsaturated polyglycolyzed glycerides, glyceryl monolinoleate, Crill #4, decaglyceryl decaoleate, triisostearin PEG 6 esters, triglyceryl monoleate, glyceryl monooleate, sorbide dioleate, polyoxyethylene castor wax, polyglycolysed glycerides, polyglycolysed glycerides, saturated C8-C10 polyglycolysed glycerides, polyoxyethylene (20) sorbitan monooleate, polyoxyethylene (20) sorbitan trioleate, copolymers of

propylene oxide and ethylene oxide, copolymers of propylene oxide and ethylene oxide, polyoxyl 35 castor oil, palm kernelamide DEA, polyoxyethylene 4 lauryl ether, polyoxyethylene (20) isohexadecyl ether, sorbitan monolaurate, alcohol ethoxylate, polyoxyethylene 80 sorbitan monolaurate, hexaglyceryl dioleate, polysorbate 80, sucrose laurate, quaternary ammoniun salt, polyoxyethylene sorbitol hexaoleate, caprylic/capric acid partial glyceride-6 EO, polyglyceryl 4 oleate.

8. A composition of claim 7 wherein at least one of said surfactants is selected from triglyceride of caprylic/capric acid, polyglycolysed glycerides, propylene glycol laurate, glyceryl monooleate, triglyceryl monoleate, mono/diglycerides of caprylic/capric acid in glycerol, saturated C8-C10 polyglycolysed glycerides, polyoxyethylene (20) sorbitan monooleate, copolymers of propylene oxide, copolymers of propylene oxide and ethylene oxide, polyoxyl 35 castor oil, polyoxyethylene 4 lauryl ether, sorbitan monolaurate, alcohol ethoxylate.

9. A composition of claim 1 wherein said oil is selected from distillated acetylated monoglycerides, distillated acetylated monoglycerides, propylene glycol and mono/di-caprylate, polyoxypropylene (15) stearyl alcohol, glyceryl tricaprylate/caprate, triglyceride of caprylic/capric acid, olive oil, caprylic/capric triglycerides, sesame oil, oleyl alcohol.

10. A composition of claim 9 wherein said oil is selected from distillated acetylated monoglycerides, distillated acetylated monoglycerides, and propylene glycol and mono/di-caprylate

11. A delivery system comprising a composition of claim 1.

12. A delivery system of claim 11 wherein said delivery system is an emulsion.

13. A delivery system of claim 11 wherein said delivery system is a capsule.

14. A method of treating hyperlipidemia comprising the administration of a composition of claim 1 to a patient.

15. A method of treating hyperlipidemia comprising the administration of a composition of claim 3 to a patient.

16. A method of treating hyperlipidemia comprising the administration of a composition of claim 11 to a patient.

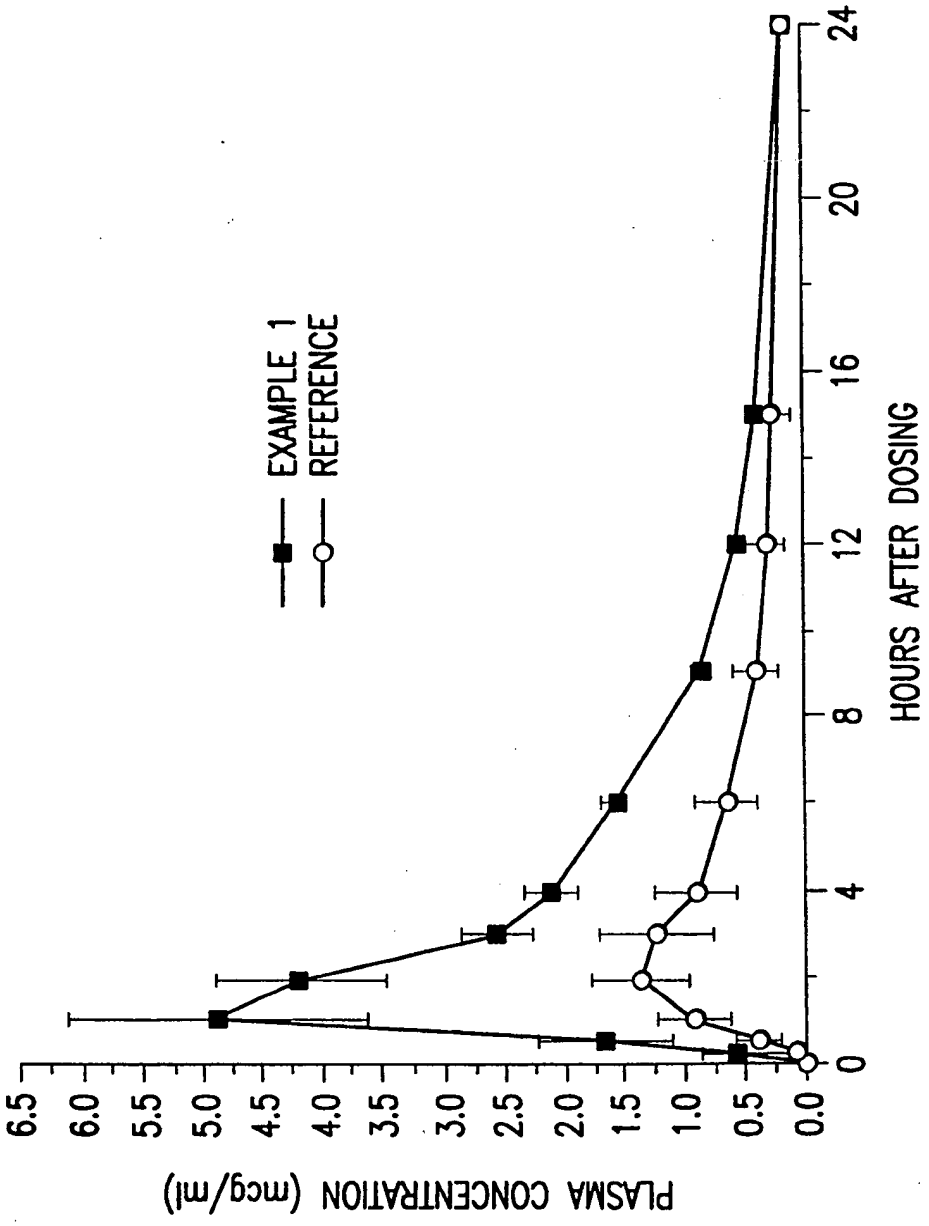
EXAMPLE 1
REFERENCE
PLASMA CONCENTRATION (mcg/ml)
HOURS AFTER DOSING
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
0
4
8
12
16
20
24

FIG. 1

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(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
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18 January 2001

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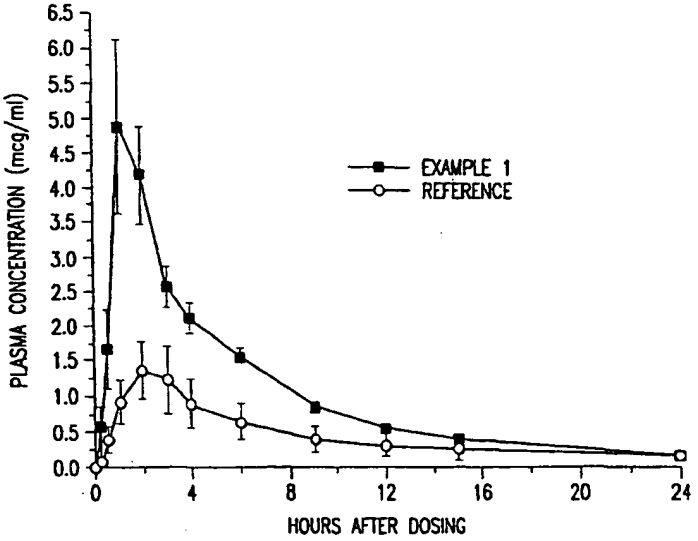

(57) Abstract: The present invention is directed to a formulation comprising a lipid-regulating agent dissolved in a mixture of an oil and one or more surfactants to form a concentrate. This concentrate forms fine and stable emulsions upon gentle mixing with water or any aqueous solutions.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/44 A61P3/06 A61K31/19 A61K31/216 A61K31/22
A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 24893 A (R.P.SCHERER LTD.,GB) 21 September 1995 (1995-09-21) cited in the application claims page 9, line 7 -page 11, line 11 page 14, line 1 -page 15, line 14 page 18, line 5 -page 19, line 1 page 25, line 3 - line 4 page 44, line 20 - line 25	1-3,7,9, 11-16
X,P	WO 99 29300 A (RTP PHARMA INC.,CA) 17 June 1999 (1999-06-17) claims examples 1-11 page 6, line 11 -page 7, line 3 page 7, line 10 -page 8, line 17 page 9, line 4 - line 10	1-3,7,9, 11-16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
9 October 2000	16/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 12528 A (SMB TECHNOLOGY,BE) 18 March 1999 (1999-03-18) claims example 1	1-16
A	EP 0 336 298 A (E.R.SQUIBB & SONS INC.,U.S.A.) 11 October 1989 (1989-10-11) cited in the application claims	1,4-6, 11-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

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